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NEPHROLOGY FORUM

Prostatitis

Principal discussant: EDWIN M. MEARES, JR.

Division of Urology, Tufts University School of Medicine, and Department of Urology, New England Medical Center, Boston, Massachusetts

Case presentations

Patient 1. A 45-year-old man described a history of recurrent urinary tract infections during the 6 years preceding his first visit to the New England Medical Center Hospital (NEMCH). The initial infection was characterized by acute chills and fever, low-back pain, urinary frequency, urgency, nocturia, dysuria, and a decrease in the force and caliber of the urinary stream. An intravenous urogram was normal and his infection responded to therapy with an antibiotic. During the ensuing 5 years he experienced similar episodes of recurrent symptomatic infection about once yearly. Each time, the symptoms abated following short courses of antibiotic therapy. During the 5 months that immediately preceded his referral, he experienced three separate episodes of symptomatic urinary tract infection.

When examined initially, he was asymptomatic while taking ampicillin orally. Physical examination disclosed normal external genitalia and modest symmetrical enlargement of the prostate without nodules. Laboratory findings included a hematocrit of 40% and a serum creatinine of 1.0 mg/dl. The urine spun sediment was normal, but bacteriologic localization cultures were positive for prostatic infection due to *Escherichia coli* (serogroup 04), and were sensitive to several antimicrobial agents, including ampicillin and trimethoprim-sulfamethoxazole (Table 1). The titer of serum antibody against this 04 *E. coli* was elevated (1:1280). An intravenous urogram was normal.

After additional cultures confirmed a diagnosis of prostatitis due to 04 *E. coli*, therapy was initiated with two tablets orally of trimethoprim-sulfamethoxazole (TMP-SMX), twice daily. During a 12-week course of treatment, the patient remained asymptomatic and all cultures remained sterile (Table 1). Throughout a 7-month follow-up, he remained asymptomatic and had sterile cultures while he was taking no medication. The titer of serum antibody against the 04 *E. coli* also fell to normal (1:160).

Patient 2. A 66-year-old man first experienced a febrile urinary tract infection due to *E. coli* several days after an indwelling urethral catheter inserted during elective abdominal surgery was removed. He initially responded to therapy with ampicillin but relapsed with a recurrent febrile urinary tract infection due to *E. coli* a few days after completion of antibiotic therapy.

He was examined initially at the NEMCH and on the sixth day of repeat therapy with ampicillin was asymptomatic. Physical findings disclosed normal external genitalia and moderate symmetrical enlargement of the prostate without nodules. Laboratory findings included a hematocrit of 42.5% and a serum creatinine of 1.1 mg/dl. The urine spun sediment was normal and bacteriologic localization cultures proved prostatitis due to *E. coli* (serogroup 04) that was sensitive to several antimicrobial agents, including ampicillin and TMP-SMX (Table 2). The titer of serum antibody against this 04 *E. coli* was elevated (1:2560). An intravenous urogram was normal and specifically excluded prostatic calcifications and significant postvoid residual.

Therapy was initiated with TMP-SMX, two tablets orally, twice daily. Throughout a 12-week course of therapy, the patient remained essentially asymptomatic; however, prostatic cultures remained positive for 04 *E. coli*, and the serum antibody titer against the 04 *E. coli* remained elevated (1:2560) (Table 2).

Patient 3. A 50-year-old man was evaluated at the NEMCH because of urinary frequency, urgency, and dysuria. About 10 years previously he had undergone surgical removal of a large bladder calculus in Brazil. He was unaware of any subsequent genitourinary tract difficulties. Physical examination disclosed a small but firm and moderately tender prostate. Laboratory findings revealed the following: hematocrit, 47%; BUN, 16 mg/dl; and serum creatinine, 1.0 mg/dl. The urine spun sediment showed pyuria (50 to 60 white blood cells per high-power field), and a culture of midstream urine grew more than 100,000 *Klebsiella pneumoniae* per ml; the organism was sensitive to sulfonamides, cephalosporin, nitrofurantoin, tetracycline, gentamicin, kanamycin, and chloramphenicol. An intravenous urogram was normal, except for multiple prostatic calculi and minimal postvoid residual.

Throughout the ensuing 4 years, the patient experienced relapsing bacteriuria due to *K. pneumoniae* despite prolonged therapy with various appropriate antimicrobial agents (Table 3). Two years ago, bacteriologic localization cultures confirmed a diagnosis of chronic calculous prostatitis due to *K. pneumoniae* (Table 3). He eventually developed exfoliative skin eruptions during therapy with nitrofurantoin, cephalexin, and possibly TMP-SMX.

Six months ago, while the patient was receiving intravenous gentamicin therapy, an uncomplicated transurethral resection of the prostate was performed. Resection included all intracapsular tissue and multiple prostatic calculi, several of which were recovered for stone culture. Cultures confirmed infection of the inner portions of the calculi with *K. pneumoniae* (Table 3). Postoperative x-ray films of the pelvis disclosed no residual calculi. The patient was discharged from the hospital on the fourth postoperative day on therapy with TMP-SMX. This medication was discontinued 2 weeks later because of skin eruptions. Subsequent follow-up confirmed apparent cure of the chronic genitourinary tract infection.

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Table 1. Chronic prostatitis cured by medical therapy

Days on (+) or off (−) drug	Colonies per ml[a]				Antibody titers
	VB1[b]	VB2[c]	EPS[d]	VB3[e]	
+2 Ampicillin	140	30	3000	410	
+9 Ampicillin	0	0	100	0	
−5 Ampicillin	2500	3000	5000	1500	
−12 Ampicillin	20	10	100	20	1:1280
+14 TMP-SMX[f]	0	0	0	0	
+36 TMP-SMX	0	0	0	0	1:1280
+57 TMP-SMX	0	0	0	0	1:1280
+93 TMP-SMX	0	0	0	0	1:640
−41 TMP-SMX	0	0	0	0	1:640
−76 TMP-SMX	0	0	0	0	1:320
−95 TMP-SMX	0	0	0	0	1:320
−123 TMP-SMX	0	0	0	0	
−196 TMP-SMX	0	0	0	0	1:160

[a] All organisms cultured were *E. coli*.
[b] VB1 refers to the first voided 10 ml of urine (urethral culture).
[c] VB2 refers to midstream aliquot (bladder culture).
[d] EPS refers to expressed prostatic secretions (prostatic culture).
[e] VB3 refers to the first voided 10 ml of urine after prostatic massage (prostatic culture).
[f] TMP-SMX refers to trimethoprim-sulfamethoxazole.

Table 2. Chronic prostatitis not cured by medical therapy

Days on (+) or off (−) Drug	Colonies per ml[a]				Antibody titer
	VB1	VB2	EPS	VB3	
No medication	—	100,000	—	—	
−8 Ampicillin	—	100,000	—	—	
+2 Ampicillin	—	0	—	—	
+4 Ampicillin	—	0	—	—	
+5 Ampicillin	—	0	—	—	
+6 Ampicillin	40	0	100,000	1,000	1:2560
+10 Ampicillin	0	0	10,000	70	
+28 TMP-SMX	20	0	6,000	10	1:2560
+56 TMP-SMX	530	200	40,000	2,000	1:2560
+84 TMP-SMX	1000	200	30,000	1,000	1:2560

[a] All organisms cultured were *E. coli*.

Discussion

DR. EDWIN M. MEARES, JR. *(Charles M. Whitney Professor and Chairman, Division of Urology, Tufts University School of Medicine; Chairman, Department of Urology, New England Medical Center Hospital, Boston, Massachusetts)*: These 3 patients illustrate some of the features of chronic bacterial prostatitis as well as the efficacy of various therapies. Patient 1 demonstrates cure by medical therapy of chronic prostatitis caused by 04 *E. coli*; Patient 2 is an example of a failure of medical therapy to cure chronic prostatitis caused by 04 *E. coli*; Patient 3 illustrates failure of medical therapy but cure by surgical treatment of chronic calculous prostatitis caused by *Klebsiella pneumoniae*.

Chronic prostatitis is a common but confusing syndrome. Most of the confusion stems from the common misconception that prostatitis is a single disease. To the contrary, a variety of inflammatory diseases of the prostate are recognized today (Table 4).

Nonbacterial prostatitis

Nonbacterial prostatitis, a condition of uncertain cause, is the most common variety of prostatic inflammation. Although the symptoms of chronic bacterial prostatitis and nonbacterial prostatitis often are indistinguishable, and the prostatic expressate in both conditions contains abnormal numbers of inflammatory cells, by definition no pathogens can be identified in patients who have nonbacterial prostatitis. A search for pathogens in cases of apparent nonbacterial prostatitis seemingly has ruled out infection caused by aerobic and anaerobic bacteria, fungi, parasites, viruses, and mycoplasmas or ureaplasmas [1–8]. Although speculation abounds that nonbacterial prostatitis actually represents infection caused by *Chlamydia trachomatis*, there are no proven cases of prostatitis caused by this class of organism. Indeed, a recent study using cultures and serologic tests in 53 men having nonacute, nonbacterial prostatitis failed to disclose a causative role for *C. trachomatis* [9].

Some patients who complain of symptoms of prostatitis, especially "prostatic pain," have no apparent prostatic inflammation, and their prostatic expressates are normal by microscopy and culture; these men suffer from prostatodynia [10]. This syndrome probably also results from a number of different causes. In some patients with prostatodynia, urodynamic testing reveals voiding abnormalities suggestive of bladder-sphincter dyssynergia; these patients often respond to therapy with

Table 3. Chronic calculous prostatitis in a 50-year-old man

Days on (+) or off (−) drug	Colonies per ml[a]			
	VB1	VB2	EPS	VB3
First visit	—	100,000	—	—
−4 Sulfisoxazole	—	100,000	—	—
+21 Nitrofurantoin	—	0	—	—
−74 Nitrofurantoin	—	100,000	—	—
+42 TMP-SMX	—	0	—	—
−112 TMP-SMX	—	100,000	—	—
−10 Sulfisoxazole	—	100,000	—	—
−30 Sulfisoxazole	—	100,000	—	—
−20 Sulfisoxazole	—	100,000	—	—
−14 Sulfisoxazole	—	100,000	—	—
+63 TMP-SMX	—	0	—	—
+163 TMP-SMX	—	0	—	—
−353 TMP-SMX	—	100,000	—	—
−60 Sulfisoxazole	—	100,000	—	—
−30 TMP-SMX	—	100,000	—	—
−184 TMP-SMX	—	100,000	—	—
+33 Cephalexin	—	0	—	—
+60 Cephalexin	—	0	—	—
−14 Cephalexin	—	100,000	—	—
+33 Cephalexin	50	0	100,000	5,000
+74 Cephalexin	10	0	50,000	1,000
−10 Cephalexin	—	100,000	—	—
−7 Cephalexin	—	100,000	—	—
−83 Cephalexin	—	100,000	—	—
−162 Cephalexin	—	100,000	—	—
+1 Gentamicin Day of surgery (CB = 0)[b] Prostatic calculi:[c] Wash 1 = 400/ml Wash 4 = 300/ml Ground calculi = 100,000/ml				
+2 Gentamicin	—	0	—	—
−1 Gentamicin	—	0	—	—
+14 TMP-SMX	—	0	—	—
−94 TMP-SMX	0	0	—	0
−171 TMP-SMX	0	0	—	0

[a] All organisms cultured were *K. pneumoniae*.
[b] CB refers to catheterized bladder.
[c] Stones were washed and cultured to determine whether the stones were infected (see Ref. 16).

alpha blockers such as phenoxybenzamine; other patients experience tension myalgia of the pelvic floor [11, 12] and respond best to treatment with diathermy, muscle relaxants, and physiotherapy; in still others, emotional problems appear to be primary and psychiatric consultation is warranted.

Given that the underlying cause of nonbacterial prostatitis is not known, it is not surprising that its cure is difficult. In such cases therapy is best directed toward symptomatic relief. The liberal use of hot sitz baths is uniformly helpful. During symptomatic flareups, other useful therapies include the short-term use of anticholinergic, analgesic, and antiinflammatory agents. Although some clinicians advocate the use of "therapeutic" prostatic massage, the benefits of such therapy are questioned by many. If one suspects infection due to ureaplasma or chlamydia, a therapeutic trial using a tetracycline preparation or erythromycin in maximal dosage is reasonable. Our preference is minocycline, 100 mg orally twice daily for 14 days, or erythromycin, 500 mg orally four times daily for 14 days. Unless the response is favorable, however, further use of antibiotics seldom is warranted. Subtotal prostatectomy is not generally indicated in the treatment of nonbacterial prostatitis because symptoms are often worse after surgery.

Bacterial prostatitis

Etiology and pathogenesis. The causative agents in bacterial prostatitis are similar in type and prevalence to those responsible for urinary tract infection. Infections caused by common strains of *Escherichia coli* predominate, although infections caused by species of proteus, klebsiella, enterobacter, pseudomonas, serratia, and other less common types of Gram-negative organisms are sometimes found [13, 14]. Mixed infections, caused by two or more strains or classes of bacteria, are not rare. Although the role of Gram-positive bacteria as causative agents in prostatitis is controversial, most studies indicate that only enterococcus *(Streptococcus fecalis)* plays an important causative role [15].

The pathogenesis of bacterial prostatitis is often unclear. Possible routes of infection include *(1)* ascending urethral infection; *(2)* reflux of infected urine into prostatic ducts that empty into the posterior urethra; *(3)* invasion by rectal bacteria via direct extension or lymphogenous spread; and *(4)* hematogenous infection.

Gonococcal and nongonococcal urethritis develop in males by ascending infection after vaginal inoculation of the urinary

Table 4. Types of prostatitis

Common forms
Nonbacterial
Acute bacterial
Chronic bacterial
Chronic calculous
Uncommon forms
Gonococcal
Tuberculous
Parasitic
Mycotic
Nonspecific granulomatous
Noneosinophilic variety
Eosinophilic variety
Suspected but unproved forms
Ureaplasma or mycoplasma
Chlamydiae
Viral

meatus during sexual intercourse. Gonococcal prostatitis occurs only in men who have histories of gonococcal urethritis. A similar pathogenesis may explain some other forms of prostatitis. The male sexual partners of women who have pathogenic coliforms in their vaginal cultures often show the same bacteria in their urethral cultures [16]. These men usually are asymptomatic, and their urethral cultures often revert to normal spontaneously. Stamey and Blacklock have noted the concomitant occurrence of identical strains of coliforms in prostatic fluid cultures in men with chronic bacterial prostatitis and in vaginal cultures from their female sexual partners [16, 17]. Substantiating data are needed to confirm the relative frequency of this mode of infection in the pathogenesis of bacterial prostatitis.

Reflux of infected urine into the prostatic ducts that empty through the posterior urethra might be an important route of infection. This possibility is supported by the recent observation that many prostatic calculi contain material commonly found in urine but foreign to prostatic secretions [18]. This finding indicates that urine enters the prostatic ducts, presumably by reflux, and initiates or participates in stone formation. If urethroprostatic reflux occurs commonly, this mechanism might prove a frequent pathway by which urinary tract bacteria reach and infect the prostate.

Methods of diagnosis. Much of the confusion about prostatitis relates to imprecise diagnostic methods. History, physical findings, and excretory urography, cystourethroscopy, and routine urinalysis often are not diagnostic. Microscopic examination of the prostatic expressate, although an important diagnostic aid, can be misleading. Inflammatory cells originating from the urethral surface, not the prostate, can contaminate the prostatic expressate as it passes through the urethra to the meatus during massage. To localize the site of inflammation, the clinician always should compare the microscopic appearance of the prostatic expressate with smears of the spun sediment of the first voided 10 ml of urine (urethral specimen) and the midstream urine (bladder specimen).

Although opinions differ regarding the number of leukocytes in expressed prostatic secretions that comprise an abnormal specimen, most recent studies indicate that prostatic secretions normally contain fewer than 10 white blood cells per high-power field [15, 19]. Expressates most indicative of prostatic inflammation manifest leukocytosis (more than 10 white blood cells per high-power field) and contain abnormal numbers of lipid-laden macrophages [15]. Moreover, the finding of macrophages in the expressate identifies the site of inflammation as the prostate, as macrophages are not found in urethral exudates.

Isolated culture of the prostatic expressate can be misleading for the same reason: urethral organisms of nonprostatic origin may contaminate the prostatic fluid as it passes through the urethra. Isolated analysis or culture of the ejaculate also can be misleading: not only is urethral contamination possible, but the semen is composed of fluids from various organs and sites. Cytologic examination of the ejaculate is complicated by the close resemblance of immature sperm cells and leukocytes. Quantitative culture of the semen may be useful in diagnosing bacterial prostatitis when prostatic fluid is difficult to obtain by massage. Proper interpretation of results, however, requires preliminary collection of urethral and bladder specimens for comparative quantitative cultures.

Immune response. Serologic studies have demonstrated an immune response in patients with bacterial prostatitis. When studied by a method of 0-specific direct bacterial agglutination, 82% of men with chronic prostatitis due to various strains of *E. coli* had elevated serum antibody titers against their prostatic pathogens, whereas men with urethritis due to *E. coli* and normal men had uniformly low serum antibody titers against urethral and fecal *E. coli,* respectively (Fig. 1) [20]. Furthermore, a return to normal of previously elevated serum antibody titers has been observed in men cured of chronic prostatitis due to *E. coli,* whereas serum titers remained elevated in men in whom treatment failed [21]. Jones [22] and Thomas, Shelokov, and Forland [23] found that chronic bacterial prostatitis usually produces a positive immunofluorescent test for antibody coating of bacteria in the urine. Gray, Billings, and Blacklock used techniques of immunodiffusion and immunoelectrophoresis to demonstrate significant elevations of IgG, IgA, and IgM in the prostatic fluid of men with chronic prostatitis [24]. It is likely that additional investigation of the immune response in prostatitis will lead to improved methods of diagnosis and better markers of disease activity.

Quantitative bacteriologic localization cultures. The performance of simultaneous quantitative cultures of the urethra, bladder urine, and expressed prostatic secretions is the most useful method of establishing the diagnosis of bacterial prostatitis. We have reported previously on the details concerning specimen collection, culture methodology, and interpretation of results and will simply summarize them here [13, 14, 25]. The voided urine and expressed prostatic secretions are collected as segmented specimens: the first voided 10 ml (VB1, voided bladder 1), the midstream aliquot (VB2), the prostatic expressate obtained by prostatic massage (EPS, expressed prostatic secretions), and the first voided 10 ml immediately after prostatic massage (VB3). All specimens are cultured quantitatively by surface streaking 0.1 ml onto blood and MacConkey agar plates. In our view, the diagnosis of prostatic infection is confirmed when the bacterial colony counts of the prostatic specimens (EPS and VB3) exceed those of the urethral (VB1)

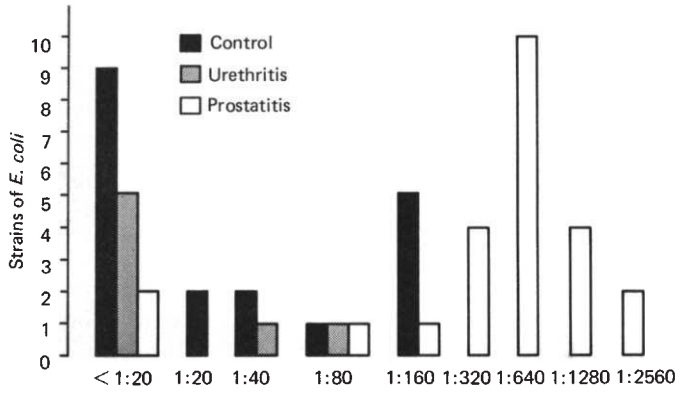

Fig. 1. *Serum antibody titers of* E. coli *in normal men and men with urethritis or prostatis.*

and bladder (VB2) specimens by at least 1 logarithm. The patients discussed today illustrate the diagnostic usefulness of this technique.

Acute bacterial prostatitis. Acute bacterial prostatitis produces such characteristic signs and symptoms that the diagnosis is usually obvious. Typically the patient experiences sudden chills, fever, low-back and perineal pain, and general malaise and prostration. Arthralgia and myalgia are common symptoms, as are intense irritative voiding symptoms (urgency, frequency, nocturia, and dysuria) and varying degrees of bladder outlet obstruction. Rectal examination reveals a markedly tender prostate that feels swollen, indurated, and warm. Although the prostatic expressate is purulent in acute prostatitis and usually yields confluent growth of the pathogen on culture, massage of an acutely inflamed prostate is an unwise procedure because of patient discomfort and the risk of bacteremia. Given that acute bacterial prostatitis is quickly followed by acute cystitis in most cases, the pathogen usually can be identified by culturing the voided urine.

Hospitalization and general supportive measures such as hydration, antipyretics, analgesics, bed rest, and stool softeners are usually required. Since urethral instrumentation should be avoided, urinary retention requiring bladder drainage should be managed by percutaneous placement of a suprapubic catheter rather than by an indwelling urethral catheter.

The diffuse, intense inflammation of acute prostatitis probably alters pharmacologic response sufficiently to allow many drugs that normally are excluded to diffuse readily into prostatic fluid. We still prefer to initiate antibacterial therapy with TMP-SMX, however. We use 160 mg of TMP and 800 mg of SMX twice daily until the results of culture and sensitivity testing are available. If the pathogen is sensitive and the clinical response is favorable, we continue therapy with this dose for at least 30 days in the hope of preventing chronic prostatitis. Alternatively, therapy can be initiated with gentamicin or tobramycin, 3 to 5 mg/kg per day, divided into 3 intramuscular or intravenous doses, plus ampicillin, 2 gm given intravenously every 6 hours. A suitable oral antimicrobial agent should be substituted after 1 week and given in full dosage for at least 30 days. Although most patients with acute bacterial prostatitis are cured by medical therapy, some develop chronic prostatitis.

Chronic bacterial prostatitis. Despite its highly variable clinical features, chronic bacterial prostatitis is a common cause of relapsing urinary tract infection in men. Many patients deny preceding bouts of acute prostatitis; some men are diagnosed only because asymptomatic bacteriuria is found incidentally; most patients experience variable irritative voiding symptoms and pain perceived at various sites (suprapubic, perineal, low back, scrotal, penile, or inner thigh areas). Some complain of postejaculatory pain and/or experience intermittent hemospermia. Chills or fever are unusual unless an acute exacerbation of the chronic infection occurs. A boggy or tender prostate is not diagnostic of chronic bacterial prostatitis. Recurrent epididymitis often denotes an underlying prostatic infection, especially in men over the age of 35.

The most characteristic feature of chronic bacterial prostatitis is relapsing bacteriuria in which the same pathogen is found repeatedly. The organism persists in prostatic fluid despite therapy with most antibacterial agents because most drugs diffuse poorly from plasma into prostatic ducts and acini. Even though the urine can be sterilized and symptoms may be controlled during therapy, cessation of medication eventually leads to reinfection of the urine and recurrent symptoms. As demonstrated in the patients presented today, treatment failures seldom are associated with alterations in type or sensitivity of the infecting organism.

Chronic calculous prostatitis. Prostatic calculi develop commonly in middle-aged and elderly men. About 20 years ago, Fox reviewed pelvic x-ray films of 3510 men whose average age was 56 years; he noted prostatic stones in about 14% [26]. The true incidence of prostatic stones obviously is much higher, as many such calculi are not visible on x-ray films. Indeed, Fox examined a large number of autopsy and surgical specimens and concluded that tiny prostatic stones can be found in virtually every adult prostate. Although these stones can cause shedding of inflammatory cells into prostatic secretions, they generally are harmless and produce no symptoms as long as they are confined to the gland and its ducts. However, in certain men with prostatic stones and relapsing bacteriuria, bacterial pathogens within the calculi have proved to be the source of the relapsing bacteriuria [27]. Similar to infected kidney stones, such prostatic calculi are impregnated to the core with bacteria that are totally protected from contact with antimicrobial agents. As in Patient 3, successful removal of these infected calculi by surgical means is the only chance for cure.

Little is known about the formation and significance of prostatic calculi. However, urethroprostatic reflux of urine might play an important role in stone formation and the pathogenesis of bacterial prostatitis. Moreover, unrecognized infected calculi might play a more important role than do unfavorable pharmacokinetics in our inability to cure chronic bacterial prostatitis by antimicrobial therapy.

Prostatic dysfunction. The profound alteration in the composition of prostatic fluid in patients with chronic bacterial prostatitis indicates that a severe, generalized secretory dysfunction is present (Table 5). This secretory dysfunction almost certainly influences the passage of antimicrobial agents into prostatic fluid, particularly as the secretions become more alkaline than normal. The difference in pH of plasma and prostatic fluid is thought to be a critically important factor influencing the nonionic diffusion of drugs from plasma across the lipid membrane of prostatic epithelium. Recent studies indicate that

Table 5. Prostatic fluid alterations in bacterial prostatitis[a]

Increased
1. pH
2. Ratio of LDH isoenzyme 5 to LDH isoenzyme 1 (LDH-5/LDH-1 = ≥ 2)
Decreased
1. Specific gravity
2. Prostatic antibacterial factor (PAF)
3. Cation concentrations (zinc, magnesium, calcium)
4. Citric acid concentration
5. Spermine concentration
6. Cholesterol concentration
7. Enzyme concentrations (acid phosphatase, lysozyme)

[a] Modified from Ref. 28.

Table 6. Prostatic fluid levels of drugs attained in normal dogs[a]

High levels	Medium-to-low levels
Rosamicin	Chloramphenicol
Trimethoprim (TMP)	Lincomycin
Clindamycin	
Erythromycin	
Oleandomycin	
Low-to-negligible levels	
Ampicillin	Oxytetracycline
Cephalothin	Penicillin G
Cephalexin	Polymyxin B
Doxycycline	Rifampin
Kanamycin	Rifamide
Minocycline	Most sulfonamides
Nitrofurantoin	Tetracycline

[a] Modified from Ref. 15.

unlike the slightly acidic or slightly alkaline pH of prostatic fluid in normal men, prostatic secretions in men with chronic bacterial prostatitis are distinctly alkaline (mean pH of 8.0 or greater) [15]. This alkaline milieu inhibits the passage of antimicrobial agents that are bases (such as TMP) into the prostatic fluid but enhances the passage of other drugs (such as minocycline).

The prostatic fluid of dogs, rats, and normal humans contains a potent prostatic antibacterial factor (PAF) that is bactericidal to most Gram-positive and Gram-negative organisms. This factor has been identified as a compound of zinc, and it probably is a zinc salt [29]. Zinc concentrations are low and PAF activity is depressed or absent in men with chronic bacterial prostatitis; some researchers believe therefore that zinc (PAF) serves as a natural defense mechanism against ascending genitourinary infection in normal men. The important question is whether men become infected because their prostatic secretions have inadequate levels of zinc (PAF) or whether zinc (PAF) is depressed as a consequence of the infection. Indeed, since the prostatic fluid concentration of all cations, not just zinc, is depressed in chronic bacterial prostatitis, the low levels of zinc might represent an effect rather than a cause of the infection. Additional studies are warranted to clarify the interrelationships of prostatic infection and secretory dysfunction of the gland. Although some clinicians advocate the use of oral zinc preparations for treating chronic bacterial prostatitis, it is not known whether the level of zinc in prostatic secretions is increased by oral administration of the substance.

Drug diffusion into prostatic fluid. Experiments performed in dogs show that most antimicrobial agents normally useful against Gram-negative pathogens diffuse poorly from plasma into prostatic fluid; a notable exception is TMP [15]. The relative levels of various drugs reaching prostatic secretions are shown in Table 6. Rosamicin, a promising new macrolide, is still under investigation by the manufacturer and currently is not available for clinical use. Assays of human prostatic tissue indicate that several antimicrobial agents achieve potentially therapeutic levels within prostatic stroma and interstitium; however, clinical studies clearly indicate that cure of chronic bacterial prostatitis correlates best with the antimicrobial level in prostatic secretions, not tissue.

The general principles that govern the transport of drugs across all human lipid membranes apply to the nonionic diffusion of antimicrobial agents from plasma across prostatic epithelium into prostatic fluid. To permeate the lipid membrane, a drug must be lipid soluble and not bound to plasma proteins. Because only the nonionized portion of a drug is lipid soluble, the dissociation constant in plasma (pKa) of the drug also is critically important in diffusion. Moreover, whether the drug is an acid or base influences diffusion, especially when the pH values of plasma and prostatic secretions differ significantly.

Diffusion experiments were performed in healthy dogs whose prostatic secretory function was assumed to be normal. The pH of prostatic secretions was measured in most animals and found uniformly slightly acidic. As noted earlier, in chronic prostatitis it is likely that reversal of the normal pH relationship between prostatic fluid and serum by increased alkalinity of the fluid alters the transport of certain drugs across prostatic epithelium. Indeed, Stamey, Bushby, and Bragonje studied the diffusion of TMP in normal dogs and observed prostatic fluid/serum ratios of 5.9 to 7.0, as compared with saliva/serum ratios of 0.7 to 0.9 [30]. The average pH of prostatic fluid in all dogs ranged from 5.7 to 6.2, as compared with the uniformly alkaline pH of saliva (7.8 to 8.8). Fair studied the diffusion of minocycline in dogs and noted higher levels in saliva (alkaline pH), as compared with prostatic fluid (acidic pH) [31].

Since increased alkalinity of the prostatic secretions is associated with chronic bacterial prostatitis, results obtained in drug diffusion experiments in dogs whose prostatic secretions are acidic cannot be used explicitly to predict clinical response of antimicrobial therapy in this condition. But until precise methods are developed that will conveniently and accurately measure antimicrobial levels in human accessory gland fluids, the results of diffusion studies characterizing prostatic fluid and salivary levels in the dog model continue to serve a useful purpose.

Medical treatment. Regardless of theoretical concerns about the concentration of TMP in excessively alkaline prostatic secretions, trimethoprim-sulfamethoxazole is the antimicrobic drug with the best documented record of success in treating chronic bacterial prostatitis. Among patients who received long-term therapy (4 to 16 weeks), the cure rates have been 32% to 71%, a rate more than twice those noted with short-term therapy (2 weeks or less) [15]. We prefer to treat patients who have susceptible pathogens with TMP-SMX, one double-strength tablet (160 mg of TMP, 800 mg of SMX), twice daily for 12 weeks. Patients who are allergic to sulfonamides or trimethoprim, or those who have azotemia, hematologic disorders, or

liver ailments might not be suitable candidates for this regimen, however.

Both erythromycin and minocycline are acclaimed as effective agents in the therapy of chronic bacterial prostatitis. The results of animal experiments suggest that each drug occasionally might attain therapeutic levels when prostatic secretions are very alkaline. Although erythromycin is inactive against Gram-negative organisms in acidic environments, alkaline environments increase its efficacy [32]. Both drugs are characterized by a high incidence of adverse side effects and neither is suitable for long-term use.

The assertion that oral carbenicillin is effective in curing chronic bacterial prostatitis requires substantiation. Preliminary studies reported by Oliveri, Sachs, and Caste seem encouraging [33]. It is unfortunate, however, that posttherapy follow-up examinations in these studies were limited to one month. Since relapses occur commonly in patients with chronic bacterial prostatitis between one and 4 months after completion of apparently successful therapy, one cannot accurately evaluate the definitive results of any treatment for this disease with follow-up examination of only one month.

Patients not cured by medical therapy usually can be managed satisfactorily by continuous suppressive therapy with low-dose medication. Preferred regimens include TMP-SMX, 1 single-strength tablet daily, or nitrofurantoin, 100 mg by mouth once or twice daily. Suppressive therapy usually controls symptoms and prevents bacteriuria. Because the pathogen persists within the prostate, however, discontinuation of therapy eventually results in recurrent symptoms and bacteriuria.

Surgical treatment. Although total prostatovesiculectomy offers the best hope for cure, postoperative sequelae such as erectile impotence and possible urinary incontinence seldom make this a desirable solution for the patient who has incurable chronic bacterial prostatitis. Provided all foci of infected tissue and calculi are removed, transurethral prostatectomy can be curative, as illustrated in Patient 3. The inflammation in chronic bacterial prostatitis occurs mainly in the peripheral portions of the gland; therefore, complete resection is required for successful results. Since many men with chronic bacterial prostatitis might have unsuspected infected calculi, careful prospective study of the role of transurethral prostatectomy in the management of medically incurable chronic bacterial prostatitis is warranted.

Questions and answers

DR. JEROME P. KASSIRER: Dr. Meares, what is the correlation between bacterial and leukocyte counts in the prostatic expressate and parenchymal infection of the prostate? How can we be confident that a patient with a positive culture and with greater than 10 leukocytes per high-power field actually has an infected gland? Do apparently normal individuals sometimes have such findings?

DR. MEARES: Although normal men can experience transient colonization of their urethral surface by small numbers of Gram-negative bacteria, such colonization seldom causes symptoms and usually disappears spontaneously. Furthermore, short-term therapy with antimicrobial agents that achieve therapeutic levels in the urine but not in the serum or prostatic fluid quickly clears these bacteria from the segmented cultures without relapse. Men who have segmented cultures indicative of prostatic infection do not clear these bacteria spontaneously and show persistently positive prostatic cultures despite prolonged therapy with appropriate antimicrobics that achieve high urinary levels and therapeutic levels in plasma but low levels in prostatic fluid. Localization cultures performed in normal male volunteers have failed to show higher counts of bacteria in prostatic specimens than in urethral specimens [16]. Indeed, even urethral colonization with pathogenic bacteria is unusual in normal men.

Current methods do not permit us to diagnose infection of the prostatic parenchyma that exists without concomitant infection of the prostatic fluid. It seems unlikely that this combination would occur, except perhaps as a consequence of hematogenous or lymphogenous spread of infection. Because pharmacokinetic studies indicate that most antimicrobial agents achieve levels in the prostatic interstitium and tissue that far exceed the drug levels in prostatic fluid, cure of parenchymal infection poses less difficulty than does cure of infection within the secretory glands and ducts.

DR. ROBERT RUBIN (*Chief of Nephrology, Lemuel Shattuck Hospital, Boston, Mass.*): With the recent availability of trimethoprim alone, would you consider changing your mode of therapy to just trimethoprim rather than its combination with sulfa?

DR. MEARES: The U.S. Food and Drug Administration has approved neither trimethoprim-sulfamethoxazole nor trimethoprim alone for specific use in the therapy of bacterial prostatitis. That agency requires proof of the drugs' efficacy that is based on prospective, randomized studies comparing these agents with other antimicrobial agents in patients with prostatitis. Although such studies are being carried out by various investigators, conclusive results are not yet available. Whether sufficient amounts of sulfamethoxazole enter prostatic fluid to enhance the antibacterial action of trimethoprim in patients with chronic bacterial prostatitis remains speculative. If there is no added advantage to administering sulfamethoxazole in combination with trimethoprim, then therapy with trimethoprim alone may prove more efficacious because the content of trimethoprim in two tablets of the combination (160 mg) is less than the content in two tablets of trimethoprim alone (200 mg).

DR. WARREN GOORNO (*Nephrologist, Emerson Hospital, Concord, Mass.*): In practice it seems that a large percentage of patients with acute prostatitis respond to many drugs, but specifically to tetracycline or ampicillin. Given your data, would you suggest using these agents as first-line drugs? My patients seem to experience intolerance to drugs like trimethoprim-sulfamethoxazole.

DR. MEARES: In cases of acute bacterial prostatitis, cure may be achieved by many of the antimicrobial agents that fail to eradicate the infecting organisms in chronic prostatitis. Theoretically, the intense inflammatory reaction accompanying acute infection alters the lipid membrane barrier that normally prevents diffusion and accumulation of certain drugs in prostatic fluid. Increased diffusion of antibiotics into prostatic fluid actually has been shown in dogs in which bacterial prostatitis has been induced experimentally [34].

Despite the probable increase in the diffusion of drugs into prostatic fluid that is associated with acute inflammation, I prefer using trimethoprim alone or in combination with sulfamethoxazole in the treatment of acute bacterial prostatitis.

Trimethoprim, which definitely accumulates in prostatic fluid, is bactericidal to most pathogens at low concentrations. In my view, an important goal of therapy in acute prostatitis is total eradication of the infecting organisms so that chronic bacterial prostatitis does not evolve. Even long-term therapy with trimethoprim-sulfamethoxazole has been tolerated exceedingly well by my patients. I believe this has been the experience of most investigators who have used this drug combination to treat a wide variety of infectious diseases.

DR. JOHN T. HARRINGTON: You mentioned that anaerobic bacteria are rarely important pathogens in prostatitis. Can this be explained by what we know about prostatic tissue metabolism or the relative oxygenation of this tissue as compared with other normal tissues in the body?

DR. MEARES: Although anaerobic bacteria commonly inhabit the urethra in men and the vagina in women, urinary tract infection due to obligate anaerobes is uncommon in both sexes. Obligate anaerobic bacteria can cause prostatitis and even prostatic abscesses; however, several studies indicate that prostatitis due to anaerobic bacteria is uncommon [1, 2, 6]. The reason why anaerobic bacteria are infrequent pathogens in prostatitis and urinary tract infections is unclear. I know of no studies that have investigated the possible role of oxygenation of prostatic tissue or secretions in the pathogenesis of infection.

DR. HARRINGTON: Would you comment further on urodynamic studies performed in men with prostatodynia?

DR. MEARES: Video-urodynamic studies performed in normal men show synergistic activity between the bladder musculature and the external sphincter mechanism during voiding. At the onset of voiding, the bladder muscle contracts, the bladder neck opens, and the external sphincter relaxes, permitting unobstructed flow. Bladder-sphincter dyssynergia, characterized by failure of relaxation or even increased activity of the external sphincter mechanism as the bladder muscle contracts during voiding, results in an obstructed voiding pattern.

Some authorities believe that bladder-sphincter dyssynergia occurs only in patients who have diseases of the central nervous system. Recently several laboratories, including our own, have observed that many men with prostatodynia have voiding abnormalities that simulate the urodynamic findings of bladder-sphincter dyssynergia [10]. These men have no signs or symptoms of central nervous system disease and their neurologic examinations are normal. A possible explanation is that the voiding abnormality occurring in prostatodynia is an acquired phenomenon that is primarily psychosomatic. We postulate that these men experience an initial bout of urethritis or prostatitis that causes pain and discomfort during voiding. Even though the original cause of the painful voiding is cured by therapy, the subconscious mind remembers the discomfort and initiates spasm of the external sphincter mechanism at the time of bladder contraction in an effort to prevent urination. If this theory is correct, cure of this voiding abnormality might require techniques of biofeedback to help the patient "unlearn" this reflex and restore normal voiding.

DR. STEPHEN ZELMAN *(Renal Fellow, NEMCH):* When a patient has chronic bacterial prostatitis and low levels of zinc and prostatic antibacterial factor in his prostatic secretions, is there a return to normal of these and other characteristics of prostatic fluid following successful treatment?

DR. MEARES: This important question needs careful study. We are still uncertain whether men develop bacterial prostatitis because they have preexisting secretory dysfunction of the gland, or whether they acquire secretory dysfunction as a result of bacterial prostatitis. Data obtained on a few men apparently cured of chronic bacterial prostatitis by antimicrobial therapy suggest that prostatic fluid tends to become less alkaline during treatment than during the infection; however, other features of the secretions have not been studied following successful treatment.

Secretory dysfunction of the prostate might play a role in male fertility. Some researchers claim that asymptomatic infections of the prostate and seminal vesicles cause infertility in certain couples, and that fertility sometimes can be restored by elimination of the infection [15, 28]. In-vitro studies suggest that massive inocula of bacteria are necessary to impair sperm viability directly; however, seminal vesicular fluid exerts a deleterious effect on sperm in ejaculates that are devoid of normal prostatic fluid [15]. One can postulate from these observations that the secretory dysfunction in chronic prostatitis can impair fertility. Careful studies are needed to define more clearly the role of chronic bacterial prostatitis in impaired fertility.

DR. ANDREW LEVEY *(Renal Fellow, NEMCH):* What proportion of men with recurrent urinary tract infections have underlying prostatic infections as the basis of their problem?

DR. MEARES: I am not aware of any epidemiologic studies that have been designed to define conclusively the incidence of acute and chronic urinary tract infections on the basis of an underlying source of prostatic infection. No doubt men do acquire urinary tract infections without preexisting or concomitant prostatic infection. Unless these men have infected urinary stones or structural genitourinary tract abnormalities, their urinary tract infections usually respond favorably to appropriate antimicrobic therapy without relapse. When a man has no genitourinary tract abnormalities and no urolithiasis but experiences recurrent urinary tract infection with the same pathogen, our data both at Stanford and here in Boston indicate that the prostate, not the kidney, is the usual site of bacterial persistence [13, 15, 16, 25]. The three patients discussed today illustrate this point.

DR. HARRINGTON: Does your experience reflect specific referral patterns or is it indicative of unselected patients as well?

DR. MEARES: Much of our early work in prostatitis was done at the Veterans Administration Hospital in Palo Alto, California. Patient selection was minimized because the Section of Urology generally served as primary care physicians for patients presenting with urinary tract infections. Much of my practice at Stanford and here in Boston consists of unselected patients, although I confess that in recent years there has been a trend toward more complicated referrals. Most of the men whom I see with a prostatitis syndrome do not have bacterial prostatitis but suffer from nonbacterial prostatitis or prostatodynia. Regardless of concerns about patient selection, most men experiencing recurrent urinary tract infection due to a consistent pathogen have a persistent source of infection within the prostate. The pathogen persists within the acini and ducts because most antimicrobial agents fail to attain therapeutic levels in prostatic fluid. These pathogens rarely change in type or susceptibility to antibacterial agents.

DR. LEVEY: It is general practice to obtain an intravenous pyelogram to evaluate the upper urinary tract in men who have acute urinary tract infection. Should we also obtain VB1, VB2, EPS, and VB3 cultures in these patients?

DR. MEARES: I believe that acute urinary tract infection should be treated with antimicrobial drugs according to susceptibility testing and clinical response to therapy. If the signs and symptoms suggest accompanying acute bacterial prostatitis, the patient should, in my view, receive appropriate therapy for at least 30 days to prevent chronic prostatitis. During careful follow-up examinations, if the patient shows relapse of bacteriuria with the same pathogen, localization cultures should be performed to investigate the possibility of a prostatic source. I wish to emphasize, however, that proper interpretation of the comparative cultures requires careful attention to detail during collection of the segmented specimens and in culture methodology.

DR. ZELMAN: Has an association been found between stone formation in the kidneys and in the prostate? Do patients with prostatic calculi ever have metabolic disorders as the basis for their stone formation?

DR. MEARES: Several years ago, Fox suggested an interrelationship between nephrolithiasis and prostatic calculi because the incidence of prostatic calculi seemed higher in men who also had kidney stones than in men who did not [26]. To my knowledge, however, conclusive studies regarding the possible relationship of prostatic calculi to nephrolithiasis or to metabolic disorders have never been performed. Most prostatic calculi are composed of tricalcium phosphate and have a crystalline structure that is distinctly different from stones formed within the kidney. Some investigators refer to these as "endogenous" prostatic stones. Surprisingly, many prostatic calculi comprise constituents commonly found in urine but foreign to prostatic secretions. These calculi are referred to as "exogenous" prostatic stones. One might speculate that most endogenous stones form as a consequence of local factors within the prostate, whereas most exogenous stones form mainly as a result of changes in urine that are associated with metabolic alterations.

DR. ZELMAN: What is the association between prostatic stones and infection?

DR. MEARES: Most men who have prostatic stones visible on x-ray films do not have recurrent urinary tract infection or infected calculi. On the other hand, when a man has chronic bacterial prostatitis and prostatic calculi, the stones usually are impregnated with the infective pathogen. In the urinary tract, infection with organisms that split urea, notably *Proteus mirabilis*, produce marked alkalinization and the rapid formation of struvite calculi. These bacteria not only participate in stone formation but become part of the stone from surface to core. The role of infection in the formation of prostatic calculi is not clear. Most of the men whom we have treated for chronic calculous prostatitis have had infection due to various strains of *E. coli*, and not to organisms that split urea. Most likely the infection is not primarily responsible for the formation of prostatic calculi, but rather the stones form first and become secondarily infected with the prostatic pathogen.

Reprint requests to Dr. Edwin M. Meares, Jr., Department of Urology, New England Medical Center Hospital, 171 Harrison Avenue, Boston, Massachusetts 02111, USA

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